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20350 7590 03/25/2008

TOWNSEND AND TOWNSEND AND CREW, LLP
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SAN FRANCISCO, CA 94111-3834

EXAMINER	
WALICKA, MALGORZATA A	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/25/2008

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/471,669	12/24/1999	JOHN P. ANDERSON	015270-006430US	7795

TITLE OF INVENTION: BETA-SECRETASE ENZYME COMPOSITIONS AND METHODS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1440	$0	$1300	$1440	06/25/2008

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
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INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/471,669	12/24/1999	JOHN P. ANDERSON	015270-006430US	7795

TITLE OF INVENTION: BETA-SECRETASE ENZYME COMPOSITIONS AND METHODS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1440	$0	$1300	$1440	06/25/2008

EXAMINER	ART UNIT	CLASS-SUBCLASS
WALICKA, MALGORZATA A	1652	435-226000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

☐ Issue Fee

☐ Publication Fee (No small entity discount permitted)

☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

☐ A check is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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WALICKA, MALGORZATA A	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/25/2008

Determination of Patent Term Extension under 35 U.S.C. 154 (b)
(application filed after June 7, 1995 but prior to May 29, 2000)

The Patent Term Extension is 0 day(s). Any patent to issue from the above-identified application will include an indication of the 0 day extension on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Extension is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Notice of Allowability	Application No.	Applicant(s)	
	09/471,669	ANDERSON ET AL.	
	Examiner	Art Unit	
	MALGORZATA A. WALICKA	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *Amendment of Nov.30, 2007*.

2. ☒ The allowed claim(s) is/are *48,51-61,64,67-69,114-181,184-187,190-193,196-199,202-205,208-211,214-217,220-223,226-240,243-259,262-278,281-297,300-316,319-335,338-354,357-373 and 376-391*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

The amendment and terminal disclaimer filed Nov. 30, 2007 are acknowledged. Claims 1-47, 49-50, 63, 70-113, 183, 189, 195, 201, 207, 213, 219 and 225 have been previously cancelled. Claims 130, 178 and 335 have been currently amended.

Claims 48, 51-62, 64-69, 114-182, 184-188, 190-194, 196-200, 202-206, 208-212, 214-218, 220-224 and 226-391 are pending and under examination.

Detailed Action

1. Objections and rejections made in the previous action are withdrawn.

2. The terminal disclaimer filed on Nov. 30, 2007 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of the patent issued on application No. 11/090,399 has been reviewed and is accepted. The terminal disclaimer has been recorded.

The terminal disclaimer has overcome obviousness double patenting rejection of claims 178-182 that was pending in previous actions.

3. Examiner's amendment

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Please cancel claims:

62, 65, 66, 182, 188, 194, 200, 206, 212, 218, 224, 241, 242, 260, 261, 279, 280, 298, 299, 317, 318, 336, 337, 355, 356, 374, 375.

Please amend claims:

48, 51, 53, 58, 64, 67, 68, 69,

114, 115, 117, 122, 123,125,

130, 131, 133, 138, 139, 141,

146, 147, 149, 154, 155, 157,

162, 163, 165, 170, 171, 173,

178, 184, 190, 196, 202, 208,

214, 220, 240, 243, 244, 259,

262, 263, 278, 281, 282, 297,

300, 301, 316, 319, 320, 335,

338, 339, 354, 357, 358, 373,

376 and 377

to read as follows.

48. An isolated nucleic acid encoding a beta secretase, wherein the nucleic acid consists of [-] a nucleotide sequence encoding the beta secretase consisting of SEQ ID NO: 43 or [a perfectly] the full length complementary sequence thereof.

51. An expression vector[,] comprising the isolated nucleic acid of claim 48 and a promoter, wherein the nucleic acid and the promoter are operably linked, and wherein the beta secretase produced by expressing said vector consists of SEQ ID NO: 43.

53. An isolated [heterologous] cell transfected with the vector of claim 51, wherein said cell expresses [a biologically active] the beta-secretase consisting of SEQ ID NO: 43.

58. A method of producing a recombinant beta-secretase enzyme consisting of SEQ ID NO: 43, comprising culturing a cell transfected with a vector comprising a nucleic acid encoding a beta secretase, wherein the nucleic acid consists of a nucleotide sequence encoding the beta secretase consisting of SEQ ID NO: 43 or [a perfectly complementary sequence thereof] and subjecting an extract or cultured medium from said cell to an affinity matrix.

64. An isolated [heterologous cell] cell, comprising

(i) a nucleic acid molecule encoding a beta secretase, wherein the nucleic acid consists of a nucleotide sequence encoding the beta secretase consisting of SEQ ID NO: 43 [or a perfectly complementary sequence thereof];

(ii) a nucleic acid molecule encoding a beta secretase substrate molecule; and

(iii) operatively linked to (i) and (ii), a regulatory sequence effective for expression of said nucleic acid molecule in said cell.

67. The cell of claim 64, wherein said beta secretase substrate molecule is selected from the group consisting of human wild type amyloid precursor protein (APPwt), a beta-secretase cleavable fragment of APPwt comprising SEQ ID NO: 54, the Swedish mutation of APPwt (APPsw), and a beta secretase cleavable fragment[s] of APPsw comprising SEQ ID NO: 51 [thereof].

68. The [A] cell of claim 64 wherein said beta secretase substrate is selected from the group consisting of a fusion protein of maltose binging protein having the C-terminus fused to the N-terminus of the 125 amino acid carboxy–terminal sequence of APPwt, and a fusion protein of maltose binding protein having the C-terminus fused to the N-terminus of the 125 amino acid carboxy–terminal sequence of APPsw [maltose binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids of APP having the cleavage site of SEQ ID NO: 54 (MBP-C125wt) and a maltose binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (MBP-C125sw)].

114. An isolated nucleic acid encoding a beta secretase, wherein the nucleic acid consists of [comprising] a nucleotide sequence encoding the beta secretase consisting of SEQ ID NO: 58 or [a perfectly] the full length complementary sequence thereof.

115. An expression vector comprising the isolated nucleic acid of claim 114 and a promoter, wherein the nucleic acid and the promoter are operably linked, and wherein the beta secretase produced by expressing said vector consists of SEQ ID NO: 58.

117. An isolated [heterologus] cell transfected with the vector of claim 115, wherein said cell expresses [a biologically active] the beta secretase consisting of SEQ ID NO: 58.

122. An isolated nucleic acid encoding a beta secretase, wherein the nucleic acid consists of [comprising] a nucleotide sequence encoding the beta secretase consisting of SEQ ID NO: 59 or [a perfectly] the full length complementary sequence thereof.

123. An expression vector comprising the isolated nucleic acid of claim 122 and a promoter, wherein the nucleic acid and the promoter are operably linked, and wherein the beta secretase produced by expressing said vector consists of SEQ ID NO: 59.

125. An isolated [heterologous] cell transfected with the vector of claim 123, wherein said cell expresses [a biologically active] the beta secretase consisting of SEQ ID NO: 59.

130. An isolated nucleic acid encoding a beta secretase, wherein the nucleic acid consists of a nucleotide sequence encoding the beta secretase consisting of SEQ ID NO: 66 or [a perfectly] the full length complementary sequence thereof.

131. An expression vector comprising the isolated nucleic acid of claim 130 and a promoter, wherein the nucleic acid and the promoter are operably linked, and wherein the beta secretase produced by expressing said vector consists of SEQ ID NO: 66.

133. An isolated [heterologous] cell transfected with the vector of claim 131, wherein said cell expresses [a biologically active] the beta secretase consisting of SEQ ID NO: 66.

138. An isolated nucleic acid encoding a beta secretase, wherein the nucleic acid consists of a nucleotide sequence encoding beta secretase consisting of SEQ ID NO: 67 or [a perfectly] the full length complementary sequence thereof.

139. An expression vector comprising the isolated nucleic acid of claim 138 and a promoter, wherein the nucleic acid and the promoter are operably linked, and wherein the beta secretase produced by expressing said vector consists of SEQ ID NO: 67.

141. An isolated [heterologous] cell transfected with the vector of claim 139, wherein said cell expresses [a biologically active] the beta secretase consisting of SEQ ID NO: 67.

146. An isolated nucleic acid encoding a beta secretase, wherein the nucleic acid consists of [comprising] a nucleotide sequence encoding the beta secretase consisting of SEQ ID NO: 68 or [a perfectly] the full length complementary sequence thereof.

147. An expression vector comprising the isolated nucleic acid of claim 146 and a promoter, wherein the nucleic acid and the promoter are operably linked, and wherein the beta secretase produced by expressing said vector consists of SEQ ID NO: 68.

149. An isolated [heterologous] cell transfected with the vector of claim 147 wherein said cell expresses [a biologically active] the beta secretase consisting of SEQ ID NO: 68.

154. An isolated nucleic acid encoding a beta sectetase, the nucleic acid consisting of a nucleotide sequence encoding the beta secretase consisting of SEQ ID NO: 69 or [a perfectly] the full length complementary sequence thereof.

155. An expression vector comprising the isolated nucleic acid of claim 154 and a promoter, wherein the nucleic acid and the promoter are operably linked, and wherein the beta secretase produced by expressing said vector consists of SEQ ID NO: 69.

157. An isolated [heterologous] cell transfected with the vector of claim 155, wherein said cell expresses [a biologically active] the beta secretase consisting of SEQ ID NO: 69.

162. An isolated nucleic acid encoding a beta secretase, wherein the nucleic acid consists of [comprising] a nucleotide sequence encoding the beta secretase consisting of SEQ ID NO: 70 or [a perfectly] the full length complementary sequence thereof.

163. An expression vector comprising the isolated nucleic acid of claim 162 and a promoter, wherein the nucleic acid and the promoter are operably linked, and wherein the beta secretase produced by expressing said vector consists of SEQ ID NO: 70.

165. An isolated [heterologous] cell transfected with the vector of claim 163, wherein said cell expresses [a biologically active] the beta secretase consisting of SEQ ID NO: 70.

170. An isolated nucleic acid encoding a beta secretase, wherein the nucleic acid consists of [comprising] a nucleotide sequence encoding the beta secretase consisting of SEQ ID NO: 74 or [a perfectly] the full length complementary sequence thereof.

171. An expression vector comprising the isolated nucleic acid of claim 170 and a promoter, wherein the nucleic acid and the promoter are operably linked, and wherein the beta secretase produced by expressing said vector consists of SEQ ID NO: 74.

173. An isolated [heterologous] cell transfected with the vector of claim 171, wherein said cell expresses [a biologically active] the beta secretase consisting of SEQ ID NO: 74.

178. A method of producing a recombinant beta-secretase enzyme consisting of SEQ ID NO: 58, comprising culturing a cell transfected with a vector comprising a nucleic acid encoding a beta secretase, consisting of SEQ ID NO: 58 [or a perfectly complementary sequence thereof] under conditions to promote growth of said cell, and subjecting an extract or cultured medium from said cell to an affinity matrix.

184. A method of producing a recombinant beta-secretase enzyme consisting of SEQ ID NO: 59, comprising culturing a cell transfected with a vector comprising a nucleic acid encoding a beta secretase, consisting of SEQ ID NO: 59 [or a perfectly

complementary sequence thereof] under conditions to promote growth of said cell, and subjecting an extract or cultured medium from said cell to an affinity matrix.

190. A method of producing a recombinant beta-secretase enzyme consisting of SEQ ID NO: 66, comprising culturing a cell transfected with a vector comprising a nucleic acid encoding a beta secretase, consisting of SEQ ID NO: 66 [or a perfectly complementary sequence thereof] under conditions to promote growth of said cell, and subjecting an extract or cultured medium from said cell to an affinity matrix.

196. A method of producing a recombinant beta-secretase enzyme consisting of SEQ ID NO: 67, comprising culturing a cell transfected with a vector comprising a nucleic acid encoding a beta secretase, consisting of SEQ ID NO: 67 [or a perfectly complementary sequence thereof] under conditions to promote growth of said cell, and subjecting an extract or cultured medium from said cell to an affinity matrix.

202. A method of producing a recombinant beta-secretase enzyme consisting of SEQ ID NO: 68, comprising culturing a cell transfected with a vector comprising a nucleic acid encoding a beta secretase, consisting of SEQ ID NO: 68 [or a perfectly complementary sequence thereof] under conditions to promote growth of said cell, and subjecting an extract or cultured medium from said cell to an affinity matrix.

208. A method of producing a recombinant beta-secretase enzyme consisting of SEQ ID NO: 69, comprising culturing a cell transfected with a vector comprising a nucleic acid encoding a beta secretase, consisting of SEQ ID NO: 69 [or a perfectly complementary sequence thereof] under conditions to promote growth of said cell, and subjecting an extract or cultured medium from said cell to an affinity matrix.

214. A method of producing a recombinant beta-secretase enzyme consisting of SEQ ID NO: 70, comprising culturing a cell transfected with a vector comprising a nucleic acid encoding a beta secretase, consisting of SEQ ID NO: 70 [or a complementary sequence thereof] under conditions to promote growth of said cell, and subjecting an extract or cultured medium from said cell to an affinity matrix.

220. A method of producing a recombinant beta-secretase enzyme consisting of SEQ ID NO: 74, comprising culturing a cell transfected with a vector comprising a nucleic acid encoding a beta secretase, consisting of SEQ ID NO: 74 [or a perfectly complementary sequence thereof] under conditions to promote growth of said cell, and subjecting an extract or cultured medium from said cell to an affinity matrix.

240. An isolated [heterologous] cell, comprising

(i) a nucleic acid molecule encoding a beta secretase, wherein the nucleic acid consists of [comprising] a nucleotide sequence encoding the beta secretase consisting of SEQ ID NO: 58 [or a perfectly complementary sequence thereof];

(ii) a nucleic acid molecule encoding a beta secretase substrate molecule; and

(iii) operatively linked to (i) and (ii), a regulatory sequence effective for expression of said nucleic acid molecule in said cell.

243. The cell of claim 240, wherein said beta secretase substrate molecule is selected from the group consisting of APPwt, a beta secretase cleavable fragment of APPwt comprising SEQ ID NO: 54, APPsw, and a beta secretase cleavable fragment[s] of APPsw comprising SEQ ID NO: 51 [thereof].

244. The [A] cell of claim 240 wherein said beta secretase substrate is selected from the group consisting of a fusion protein of maltose binging protein having the C-terminus fused to the N-terminus of the 125 amino acid carboxy–terminal sequence of APPwt, and a fusion protein of maltose binding protein having the C-terminus fused to the N-terminus of the 125 amino acid carboxy–terminal sequence of APPsw [maltose binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids of APP having the cleavage site of SEQ ID NO: 54 (MBP-C125wt) and a maltose binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (MBP-C125sw)].

259. An isolated [heterologous] cell, comprising

(i) a nucleic acid molecule encoding a beta secretase, wherein the nucleic acid consists of [comprising] a nucleotide sequence encoding the beta secretase consisting of SEQ ID NO: 59 [or a perfectly complementary sequence thereof];

(ii) a nucleic acid molecule encoding a beta secretase substrate molecule; and

(iii) operatively linked to (i) and (ii), a regulatory sequence effective for expression of said nucleic acid molecule in said cell.

262. The cell of claim 259, wherein said beta secretase substrate molecule is selected from the group consisting of APPwt, a beta secretase cleavable fragment of APPwt comprising SEQ ID NO: 54, APPsw, and a beta secretase cleavable fragment[s] of APPsw comprising SEQ ID NO: 51 [thereof].

263. The [A] cell of claim 259 wherein said beta secretase substrate is selected from the group consisting of a fusion protein of maltose binging protein having the C-terminus fused to the N-terminus of the 125 amino acid carboxy–terminal sequence of APPwt, and a fusion protein of maltose binding protein having the C-terminus fused to the N-terminus of the 125 amino acid carboxy–terminal sequence of APPsw [maltose binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids of APP having the cleavage site of SEQ ID NO: 54 (MBP-C125wt) and a maltose binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (MBP-C125sw)].

278. An isolated [heterologous] cell, comprising

(i) a nucleic acid molecule encoding a beta secretase, wherein the nucleic acid consists of [comprising] a nucleotide sequence encoding the beta secretase consisting of SEQ ID NO: 66 [or a perfectly complementary sequence thereof].

(ii) a nucleic acid molecule encoding a beta secretase substrate molecule; and

(iii) operatively linked to (i) and (ii), a regulatory sequence effective for expression of said nucleic acid molecule in said cell.

281. The cell of claim 278, wherein said beta secretase substrate molecule is selected from the group consisting of APPwt, a beta secretase cleavable fragment of APPwt comprising SEQ ID NO: 54, APPsw, and a beta secretase cleavable fragment[s] of APPsw comprising SEQ ID NO: 51 [thereof].

282. The [A] cell of claim 278 wherein said beta secretase substrate is selected from the group consisting of a fusion protein of maltose binging protein having the C-terminus fused to the N-terminus of the 125 amino acid carboxy–terminal sequence of APPwt, and a fusion protein of maltose binding protein having the C-terminus fused to the N-terminus of the 125 amino acid carboxy–terminal sequence of APPsw [maltose binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids of APP having the cleavage site of SEQ ID NO: 54 (MBP-C125wt) and a maltose binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (MBP-C125sw)].

297. An isolated [heterologous] cell, comprising

(i) a nucleic acid molecule encoding a beta secretase, wherein the nucleic acid consists of [comprising] a nucleotide sequence encoding the beta secretase consisting of SEQ ID NO: 67 [or a perfectly complementary sequence thereof];

(ii) a nucleic acid molecule encoding a beta secretase substrate molecule; and

(iii) operatively linked to (i) and (ii), a regulatory sequence effective for expression of said nucleic acid molecule in said cell.

300. The cell of claim 297, wherein said beta secretase substrate molecule is selected from the group consisting of APPwt, a beta secretase cleavable fragment of APPwt comprising SEQ ID NO: 54, APPsw, and a beta secretase cleavable fragment[s] of APPsw comprising SEQ ID NO: 51 [thereof].

301. The [A] cell of claim 297 wherein said beta secretase substrate is selected from the group consisting of a fusion protein of maltose binging protein having the C-terminus fused to the N-terminus of the 125 amino acid carboxy–terminal sequence of APPwt, and a fusion protein of maltose binding protein having the C-terminus fused to the N-terminus of the 125 amino acid carboxy–terminal sequence of APPsw [maltose binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids of APP having the cleavage site of SEQ ID NO: 54 (MBP-C125wt) and a maltose

binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (MBP-C125sw)].

316. An isolated [heterologous] cell, comprising

(i) a nucleic acid molecule encoding a beta secretase, wherein the nucleic acid consists of [comprising] a nucleotide sequence encoding the beta secretase consisting of SEQ ID NO: 68 [or a perfectly complementary sequence thereof];

(ii) a nucleic acid molecule encoding a beta secretase substrate molecule; and

(iii) operatively linked to (i) and (ii), a regulatory sequence effective for expression of said nucleic acid molecule in said cell.

319. The cell of claim 316, wherein said beta secretase substrate molecule is selected from the group consisting of APPwt, a beta secretase cleavable fragment of APPwt comprising SEQ ID NO: 54, APPsw, and a beta secretase cleavable fragment[s] of APPsw comprising SEQ ID NO: 51 [thereof].

320. The [A] cell of claim 316 wherein said beta secretase substrate is selected from the group consisting of a fusion protein of maltose binging protein having the C-terminus fused to the N-terminus of the 125 amino acid carboxy–terminal sequence of APPwt, and a fusion protein of maltose binding protein having the C-terminus fused to the N-terminus of the 125 amino acid carboxy–terminal sequence of APPsw [maltose binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids

of APP having the cleavage site of SEQ ID NO: 54 (MBP-C125wt) and a maltose binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (MBP-C125sw)].

335. An isolated [heterologous] cell, comprising

(i) a nucleic acid molecule encoding a beta secretase, wherein the nucleic acid consists of [comprising] a nucleotide sequence encoding the beta secretase consisting of SEQ ID NO: 69 [or a perfectly complementary sequence thereof];

(ii) a nucleic acid molecule encoding a beta secretase substrate molecule; and

(iii) operatively linked to (i) and (ii), a regulatory sequence effective for expression of said nucleic acid molecule in said cell.

338. The cell of claim 335, wherein said beta secretase substrate molecule is selected from the group consisting of APPwt, a beta secretase cleavable fragment of APPwt comprising SEQ ID NO: 54, APPsw, and a beta secretase cleavable fragment[s] of APPsw comprising SEQ ID NO: 51 [thereof].

339. The [A] cell of claim 335 wherein said beta secretase substrate is selected from the group consisting of a fusion protein of maltose binging protein having the C-terminus fused to the N-terminus of the 125 amino acid carboxy–terminal sequence of APPwt, and a fusion protein of maltose binding protein having the C-terminus fused to the N-terminus of the 125 amino acid carboxy–terminal sequence of APPsw [maltose

binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids of APP having the cleavage site of SEQ ID NO: 54 (MBP-C125wt) and a maltose binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (MBP-C125sw)].

354. An isolated [heterologous] cell, comprising

(i) a nucleic acid molecule encoding a beta secretase, wherein the nucleic acid consists of [comprising] a nucleotide sequence encoding the beta secretase consisting of SEQ ID NO: 70 [or a perfectly complementary sequence thereof];

(ii) a nucleic acid molecule encoding a beta secretase substrate molecule; and

(iii) operatively linked to (i) and (ii), a regulatory sequence effective for expression of said nucleic acid molecule in said cell.

357. The cell of claim 354, wherein said beta secretase substrate molecule is selected from the group consisting of APPwt, a beta secretase cleavable fragment of APPwt comprising SEQ ID NO: 54, APPsw, and a beta secretase cleavable fragment[s] of APPsw comprising SEQ ID NO: 51 [thereof].

358. The [A] cell of claim 354 wherein said beta secretase substrate is selected from the group consisting of a fusion protein of maltose binging protein having the C-terminus fused to the N-terminus of the 125 amino acid carboxy–terminal sequence of APPwt, and a fusion protein of maltose binding protein having the C-terminus fused to

the N-terminus of the 125 amino acid carboxy–terminal sequence of APPsw [maltose binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids of APP having the cleavage site of SEQ ID NO: 54 (MBP-C125wt) and a maltose binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (MBP-C125sw)].

373. An isolated [heterologous] cell, comprising

(i) a nucleic acid molecule encoding a beta secretase, wherein the nucleic acid consists of [comprising] a nucleotide sequence encoding the beta secretase consisting of SEQ ID NO: 74 [or a perfectly complementary sequence thereof];

(ii) a nucleic acid molecule encoding a beta secretase substrate molecule; and

(iii) operatively linked to (i) and (ii), a regulatory sequence effective for expression of said nucleic acid molecule in said cell.

376. The cell of claim 373, wherein said beta secretase substrate molecule is selected from the group consisting of APPwt, a beta secretase cleavable fragment of APPwt comprising SEQ ID NO: 54, APPsw, and a beta secretase cleavable fragment[s] of APPsw comprising SEQ ID NO: 51 [thereof].

377. The [A] cell of claim 373 wherein said beta secretase substrate is selected from the group consisting of a fusion protein of maltose binging protein having C-terminus fused to N-terminus of the 125 amino acid carboxy–terminal sequence of

APPwt, and a fusion protein of maltose binding protein having C-terminus fused to N-terminus of the 125 amino acid carboxy–terminal sequence of APPsw [maltose binding protein fused at the carboxy-terminus to the 125 carboxyl-terminal amino acids of APP having the cleavage site of SEQ ID NO: 54 (MBP-C125wt) and a maltose binding protein fused at the carboxy-terminus to the 125 C-terminus amino acids of APP having the cleavage site of SEQ ID NO: 51 (MBP-C125sw)].

Authorization for this examiner's amendment was given in a telephone interview with applicants' representative Dr. J. Liebeschuetz on March 18, 2008.

4. Allowance

Claims 48, 51-61, 64, 67-69, 114-181, 184-187, 190-193, 196-199, 202-205, 208-211, 214-217, 220-223, 226-240, 243-259, 262-278, 281-297, 300-316, 319-335, 338-354, 357-373, 376-391 are allowed. The claims are directed to the DNA molecules encoding mature forms of human beta secretase of SEQ ID NO: 2 that are identified by SEQ ID NOs: 43, 66, 67 and 69. The instant claims are also directed to the DNA molecules encoding proteins being artificial variants of human beta secretase of SEQ ID NO: 2 and its mature forms of SEQ ID NOs: 43, 66, 67 and 69. The variants were obtained by truncation of C-terminus of said sequences. The mature and truncated forms of human beta secretase of SEQ ID NO: 2 are novel and nonobvious for the reasons explained during the prosecution of this and related applications that have been already patented; see particularly the notice of allowance of the application No.

09/723,722 issued on April 7, 2006. Thus, the methods of using said products claimed in the instant application are also novel and non-obvious.

> Any comments considered necessary by applicant must be submitted no later then the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed, can be reached on (571) 272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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